THE REMARKS

The Amendments

Applicants have amended the trademarks throughout the application and added the chemical names. Support for the amendments can be found, in the catalog of SIGMA (St. Louis, MO).

No new matter is added in the amendments. The Examiner is requested to enter the amendments.

Priority

The Examiner states that applicant has not filed a certified copy of European Patent Application No. 02017313.4, as required by 35 U.S.C. 119(b). Applicants submit that parent application 10/633,484 contains a certified copy of the EP application. Therefore, the requirement of 37 CFR 1.55(a)(2) is satisfied.

Objections to the Specification

Applicants have amended the specification to insert the U.S. Patent No., to amend the description of the figures, and to add the chemical names of the trademarks. Therefore, the objections to the specification should be withdrawn.

35 USC § 102(e) Rejection

Claims 1 and 3-6 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by U.S. Patent No. 6,709,832 B1, as evidenced by Geradts et al. (Am. J. Pathol. 1999 Jun; 154(6)L 1665-1671). The rejection is traversed.

The '832 Patent broadly teaches a method for detecting cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas in situ, comprising determining the overexpression of cyclin-dependent kinase inhibitor p16 in a human cervical body sample by comparing the expression level of cyclin-dependent kinase inhibitor p16 within said sample to the expression level present in a healthy human cervical body sample. The '832 Patent also illustrates the method by detecting the overexpression of p16 in biopsies of cervix uteri, where

the tissue sections were incubated with a p16 antibody and the overexpression was detected by staining the tissue sections (Example 1). However, the '832 Patent does not teach the specific method of the present invention, i.e., solubilizing the cervical body sample and detecting the overexpression of p16 in the solubilized sample. **The '832 Patent discloses a genus; however, the species of the present invention is patentable over the genus.**

The Examiner states that the '832 Patent does not expressly teach the process of determining the overexpression of p16 by lysing the cells and solubilizing the protein. Nonetheless, the Examiner states that the '832 Patent teaches the determination is made by Western blot analysis, a process briefly described by Example 2 at column 4, lines 55-67, which involves the preparation of cell extracts; and as evidenced by Geradts et al., the determination of the overexpression, which is made by Western blot, comprises the step of lysing the cells and solubilizing the protein to be detected.

Applicants respectfully disagree with the Examiner regarding the interpretation of Example 2 of the '832 Patent. Example 2 of the referenced patent showed the detection of p16 in HPV-transformed cells, not in a solubilized cervical body sample. In the Example, the cervical carcinoma cells were transformed by HPV. The cell extract of the enriched population of HPV transformed cells were collected and p16 in the cell extract was detected by Western blot. The Example demonstrates the detection of p16 in carcinoma cell lines with well known characteristics. However, the Example does not show the detection of p16 in a mixed native cell population, nor does it pertain to a method for detecting cervical carcinoma from a cervical body sample.

Geradts et al only disclose the Western blot protocol applied on cell monolayers. The disclosure does not add anything to the '832 Patent.

The present claims are directed to a method where native cells are solubilized from a healthy cervical body sample and a test cervical body sample. The overexpression of p16 is determined by comparing the p16 level within the solubilized test cervical sample with the p16 level in the solubilized healthy cervical sample. There is no pre-selection of cells to enrich or sort out certain cell types to facilitate the p16 detection.

In the present application, Applicants have described **the unexpected advantages** of the invention, which is an improvement over the '832 Patent (page 5, line 24-page 6, line 5):

> Due to the expression of cyclin dependent kinase inhibitor p16 in certain benign cell types present in cervical specimens, the diagnosis of dysplasias based on the level of cyclin dependent kinase inhibitor p16 without additional information on the cellular morphology seem to be difficult or impossible. It was known in the art that up to 30% of metaplastic cells, which may be present in cervical swabs, are immunoreactive for cyclin dependent kinase inhibitor p16 at a moderate to high level. Moreover, endometrial cells that may under certain circumstances be present in cervical swabs are positive for p16. In cytological or histological testing procedures, this fact does not influence the diagnosis, because the cell types may easily be distinguished from dysplastic cells with respect to their cellular morphology.
> Surprisingly the inventors found that by defining a threshold value of cyclin dependent kinase inhibitor p16, it is possible to enable the detection or diagnosis of dysplasias even without knowledge of the cellular morphology.

Applicants have described the conditions of solubilizing a cervical body sample to preserve the molecular properties of the sample, in which the morphological information of the sample is lost (see Application at page 7, line 24 – page 8, line 22).

Applicants have further reduced the invention to practice. Examples 3 and 4 demonstrate solubilizing human cervical swab samples in a lysis buffer, and determining the overexpression of p16 in the solubilized cervical sample. Applicants were the first who discovered that the measurement of one single marker of p16, in a lysate containing various different cell types in unknown ratios, is an indication of cervical carcinoma.

Therefore, the present invention is novel and non-obvious over the '832 Patent.

35 USC § 103(a) Rejection

a Claim 2 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. Patent No. 6,709,832 B1, as evidenced by Geradts et al., in view of Ryder et al. (Clin. Chem. 1988 Dec; 34 (12): 2513-2516.

For the same reasons as discussed above, Claim 2 is not obvious over the '832 Patent, as evidenced by Geradts et al. The addition of Ryder, which only discloses procedures of enzyme immunoassays, does not cure the deficiency of the '832 Patent.

b. Claims 1 and 3-6 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Khleif et al. (Proc. Natl. Acad. Sci. USA. 1996 Apr: 93: 4350-4354), as evidenced by Bio-Rad Protein Assay (instruction manual provided with a Bradford assay kit manufactured by Bio-Rad) and the American Type Culture Collection™ (ATCC) catalog, in view Klaes et al. (Int. J. Cancer, 2001: 92: 276-284).

Khleif et al discloses that p16 is expressed in cervical cancer cell lines in which the RB gene is not functional, either as a consequence of the mutation of RB gene or expression of the human papilloma virus E7 protein. Khleif et al also discloses that p16 levels are increased in primary cells in which RB gene has been inactivated by DNA tumor virus proteins. However, Khleif et al do not disclose that p16 is overexpressed in cervical carcinoma.

Contrary to the Examiner's assertion, Khleif et al does not teach a process comprising obtaining a cervical body sample from a human subject. A cancer cell line is not a cervical body sample as referred to in this application.

Khleif et al do not teach or suggest (i) a method for detecting cervical carcinomas, cervical intraepithelial neoplasias or cervical carcinomas in-situ from a solubilized sample of a human subject, (ii) obtaining a cervical body sample from a human subject, or (iii) determining the overexpression of cyclin dependent kinase inhibitor p16 in the solubilized cervical sample by comparing the level of cyclin dependent kinase inhibitor p16 within said solubilized cervical sample with the level present in a solubilized healthy human cervical sample.

The secondary references cited by the Examiner do not cure the deficiency of Khleif et al. Therefore, the 103(a) rejection of Claims 1 and 3-6 over Khleif et al, as evidenced by Bio-Rad Protein Assay, and ATCC catalog, in view of Klaes et al should be withdrawn.

c. Claim 2 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Khleif et al. in view of Klaes et al., as applied to claims 1 and 3-6 above, and further in view of Ryder et al.

For the same reasons as discussed above in b, the 103(a) rejection of Claim 2 should be withdrawn.

Double Patenting Rejections

a. Claims 1 and 3-6 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 in view of Khleif et al., as evidenced by Bio-Rad Protein Assay.

As discussed above, Claims 1 and 3-6 are an improvement invention, but not an obvious variation of Claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832. Therefore, the double-patenting rejection of Claims 1 and 3-6 over the '832 Patent should be withdrawn.

b. Claim 2 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over U.S. Patent No. 6,709,832 in view of Khleif et al, as evidenced by Bio-Rad Protein Assay, in further view of Ryder et al.

As discussed above, Claim 2 is an improvement invention, but not an obvious variation of claims of U.S. Patent No. 6,709,832. Therefore, the double-patenting rejection of Claim 2 over the '832 Patent should be withdrawn.

c. Claims 1 and 3-6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-26, 33, 34, and 36-40 of copending Application No. 10/633,484 in view of Klaes et al.

Applicants wish to postpone the response to this rejection until the claims are otherwise allowable.

d. Claims 1-6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 14-16, 42-50, 52-57, and 85 of copending Application No. 10/569,758.

Applicants wish to postpone the response to this rejection until the claims are otherwise allowable.

CONCLUSION

Applicants believe that the application is now in good and proper condition for allowance. Early notification of allowance is earnestly solicited.

Respectfully submitted,

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